

Appl. No. 10/606,632
Reply to Office Action of April 21, 2005

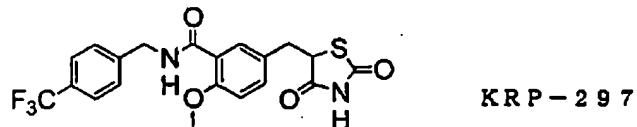
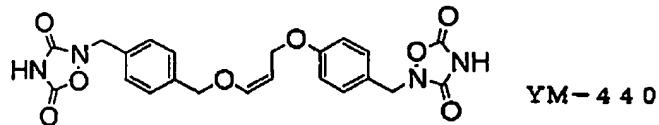
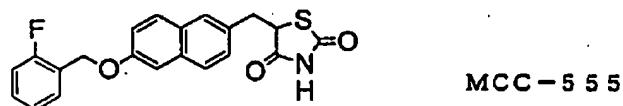
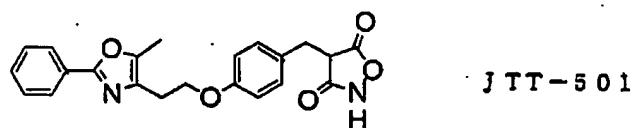
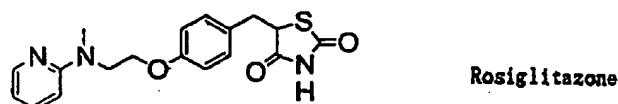
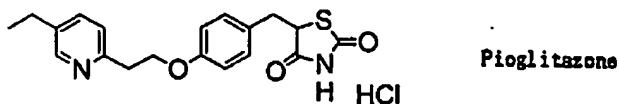
This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

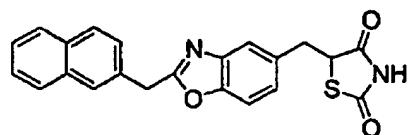
Claim 1 (Canceled).

2. (Currently Amended) A pharmaceutical composition according to Claim 1 wherein said insulin sensitizer comprises one or more compounds selected from the group consisting of troglitazone and pioglitazone, rosiglitazone, JTT-501, MCC-555, GI-262570, YM-440, KRP-297, T-174, NC-2100, BMS-298585, AZ-242 and NN-622 represented by the formula below

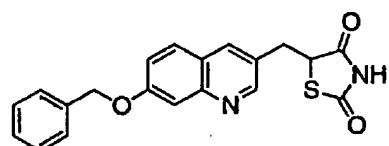
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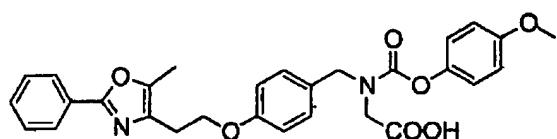
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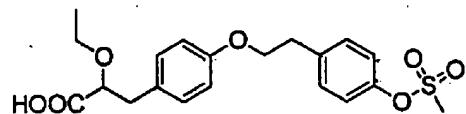
T-174



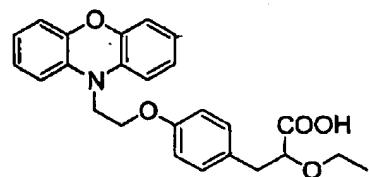
NC-2100



BMS-298585



AZ-242

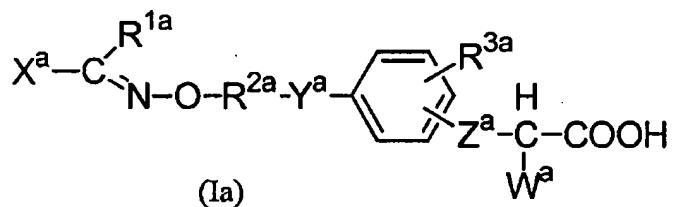


NN-622

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5-[4-(6-Methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione or a pharmacologically acceptable salt thereof,

a phenylalkylcarboxylic acid derivative having the general formula (Ia) below:



a pharmacologically acceptable salt thereof or a pharmacologically acceptable ester thereof
[wherein,

R^{1a} represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

R^{2a} represents a straight- or branched-chain alkylene group having from 2 to 6 carbon atoms,

R^{3a} represents (i) a hydrogen atom, (ii) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group

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having from 1 to 4 carbon atoms, (v) a halogen atom, (vi) a nitro group, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^a mentioned below or (ix) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety,

Z^a represents a single bond or a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

W^a represents (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a hydroxyl group, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) an amino group, (vi) a straight- or branched-chain monoalkylamino group having from 1 to 4 carbon atoms, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an N-alkyl-N-aryl amino group having a straight- or branched-chain alkyl group having from 1 to 4 carbon atoms and an aryl group

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having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (ix) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^a mentioned below, (x) an aryloxy group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (xi) an arylthio group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (xii) an arylamino group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (xiii) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (xiv) an aralkyloxy group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (xv) an aralkylthio group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (xvi) an aralkylamino group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^a mentioned below on the aryl moiety, (xvii) a 1-pyrrolyl group,

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(xviii) a 1-pyrrolidinyl group, (xix) a 1-imidazolyl group, (xx) a piperidino group or (xxi) a morpholino group,

X^a represents an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^a mentioned below or a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms which may have from 1 to 3 substituents α^a mentioned below,

the substituent α^a is selected from the group consisting of (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a straight- or branched-chain halogenated alkyl group having from 1 to 4 carbon atoms, (iii) a hydroxyl group, (iv) a straight- or branched-chain aliphatic acyloxy group having from 1 to 4 carbon atoms, (v) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (vi) a straight- or branched-chain alkylenedioxy group having from 1 to 4 carbon atoms, (vii) an aralkyloxy group having from 7 to 12 carbon atoms, (viii) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (ix) a straight- or branched-chain alkylsulfonyl group having from 1 to 4 carbon atoms, (x) a halogen atom, (xi) a nitro group, (xii) a straight-

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or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (xiii) an aralkyl group having from 7 to 12 carbon atoms, (xiv) an aryl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xv) an aryloxy group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvi) an arylthio group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4

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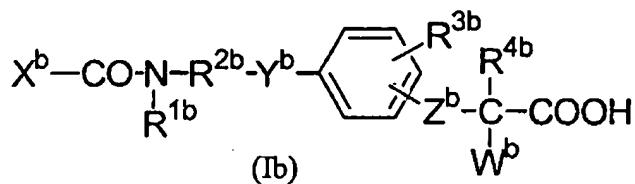
carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvii) an arylsulfonyl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xviii) an arylsulfonylamino group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms, and the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms), (xix) a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xx) a 5- to 10-membered monocyclic or bicyclic

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heteroaromatic oxy group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxi) a 5- to 10-membered monocyclic or bicyclic heteroaromatic thio group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonyl group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms and (xxiii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonylamino group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms (the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms) and

Y^a represents an oxygen atom, a sulfur atom or a group of formula: $>N-R^{4a}$ (wherein R^{4a} represents a hydrogen atom, a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms or a straight- or branched-chain aliphatic acyl group having from 1 to 8 carbon atoms or an aromatic acyl group)], a amidocarboxylic acid derivative having the general formula (Ib) below:

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a pharmacologically acceptable salt thereof or a
pharmacologically acceptable ester thereof

[wherein,

R^{1b} represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

R^{2b} represents a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

R^{3b} represents (i) a hydrogen atom, (ii) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) a halogen atom, (vi) a nitro group, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3

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substituents α^b mentioned below or (ix) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety,

R^4b represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

Z^b represents a single bond or a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

W^b represents (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a hydroxyl group, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) an amino group, (vi) a straight- or branched-chain monoalkylamino group having from 1 to 4 carbon atoms, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an N-alkyl-N-arylamino group having a straight- or branched-chain alkyl group having from 1 to 4 carbon atoms and an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (ix) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3

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substituents α^b mentioned below, (x) an aryloxy group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (xi) an arylthio group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (xii) an arylamino group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (xiii) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (xiv) an aralkyloxy group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (xv) an aralkylthio group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (xvi) an aralkylamino group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents α^b mentioned below on the aryl moiety, (xvii) a 1-pyrrolyl group, (xviii) a 1-pyrrolidinyl group, (xix) a 1-imidazolyl group, (xx) a piperidino group or (xxi) a morpholino group,
 α^b represents an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents α^b mentioned below or a

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5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms which may have from 1 to 3 substituents α^b mentioned below,

the substituent α^b mentioned above is selected from the group consisting of (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a straight- or branched-chain halogenated alkyl group having from 1 to 4 carbon atoms, (iii) a hydroxyl group, (iv) a straight- or branched-chain aliphatic acyloxy group having from 1 to 4 carbon atoms, (v) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (vi) a straight- or branched-chain alkylenedioxy group having from 1 to 4 carbon atoms, (vii) an aralkyloxy group having from 7 to 12 carbon atoms, (viii) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (ix) a straight- or branched-chain alkylsulfonyl group having from 1 to 4 carbon atoms, (x) a halogen atom, (xi) a nitro group, (xii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (xiii) an aralkyl group having from 7 to 12 carbon atoms, (xiv) an aryl group having from 6 to 10

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carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xv) an aryloxy group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvi) an arylthio group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvii) an arylsulfonyl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain

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alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xviii) an arylsulfonylamino group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms, and the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms), (xix) a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xx) a 5- to 10-membered monocyclic or bicyclic heteroaromatic oxy group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxi) a 5- to 10-membered monocyclic or bicyclic heteroaromatic thio group containing from 1 to 4 heteroatoms

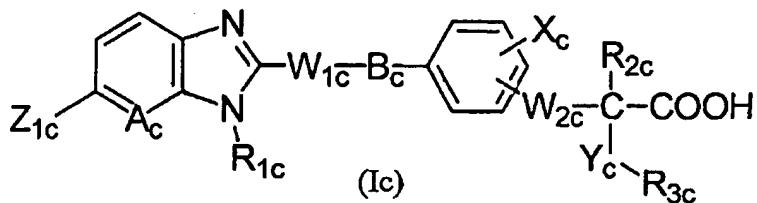
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selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonyl group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms and (xxiii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonylamino group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms (the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms) and

Y^b represents an oxygen atom, a sulfur atom or a group of formula: $>N-R^{5b}$ (wherein R^{5b} represents a hydrogen atom, a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms or a straight- or branched-chain aliphatic acyl group having from 1 to 8 carbon atoms or an aromatic acyl group)],

a α -substituted carboxylic acid derivative having the general formula (Ic) below:

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a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

R_{1c} , R_{2c} and R_{3c} are the same or different, and each represents (i) a hydrogen atom, (ii) a C_1 - C_6 alkyl group, (iii) a C_6 - C_{10} aryl group (optionally having from 1 to 5 substituents α_{1c} mentioned below), (iv) a C_7 - C_{16} aralkyl group (optionally having from 1 to 5 substituents α_{1c} mentioned below on the aryl moiety), (v) a C_1 - C_6 alkylsulfonyl group, (vi) a C_1 - C_6 halogenoalkylsulfonyl group, (vii) a C_6 - C_{10} arylsulfonyl group (optionally having from 1 to 5 substituents α_{1c} mentioned below) or (viii) a C_7 - C_{16} aralkylsulfonyl group (optionally having from 1 to 5 substituents α_{1c} mentioned below on the aryl moiety),

A_c represents a nitrogen atom or a $=CH-$ group,

B_c represents an oxygen atom or a sulfur atom,

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W_{1c} represents a C_1-C_8 alkylene group,

W_{2c} represents a single bond or a C_1-C_8 alkylene group,

X_c represents (i) a hydrogen atom, (ii) a C_1-C_6 alkyl group, (iii) a C_1-C_6 halogenoalkyl group, (iv) a C_1-C_6 alkoxy group, (v) a halogen atom, (vi) a hydroxyl group, (vii) a cyano group, (viii) a nitro group, (ix) a C_3-C_{10} cycloalkyl group, (x) a C_6-C_{10} aryl group (optionally having from 1 to 5 substituents β_c mentioned below), (xi) a C_7-C_{16} aralkyl group (optionally having from 1 to 5 substituents β_c mentioned below on the aryl moiety), (xii) a C_1-C_7 aliphatic acyl group, (xiii) a C_4-C_{11} cycloalkylcarbonyl group, (xiv) a C_7-C_{11} arylcarbonyl group (optionally having from 1 to 5 substituents β_c mentioned below), (xv) a C_8-C_{17} aralkylcarbonyl group (optionally having from 1 to 5 substituents β_c mentioned below on the aryl moiety), (xvi) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β_c mentioned below), (xvii) a carbamoyl group, (xviii) a C_7-C_{11} arylaminocarbonyl group (optionally having from 1 to 5 substituents β_c mentioned below on the aryl moiety) or (xix) an amino group (optionally having one or two substituents β_c mentioned below),

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Y_c represents an oxygen atom or a $S(O)_p$ group (wherein p is an integer of from 0 to 2),

Z_{1c} represents (i) a hydrogen atom, (ii) a C_1 - C_6 alkyl group, (iii) a C_1 - C_6 alkoxy group, (iv) a C_1 - C_6 alkylthio group, (v) a halogen atom, (vi) a C_6 - C_{10} aryl group (optionally having from 1 to 5 substituents α_1 mentioned below), (vii) a C_7 - C_{16} aralkyl group (optionally having from 1 to 5 substituents α_{1c} mentioned below on the aryl moiety), (viii) a C_6 - C_{10} aryloxy group (optionally having from 1 to 5 substituents α_{1c} mentioned below), (ix) a C_7 - C_{16} aralkyloxy group (optionally having from 1 to 5 substituents α_{1c} mentioned below on the aryl moiety), (x) a C_3 - C_{10} cycloalkyloxy group, (xi) a C_3 - C_{10} cycloalkylthio group, (xii) a saturated heterocyclic oxy group (optionally having from 1 to 5 substituents α_{1c} mentioned below), (xiii) a monocyclic heteroaromatic oxy group (optionally having from 1 to 5 substituents α_{1c} mentioned below), (xiv) a C_6 - C_{10} arylthio group (optionally having from 1 to 5 substituents α_{1c} mentioned below), (xv) a C_7 - C_{16} aralkylthio group (optionally having from 1 to 5 substituents α_{1c} mentioned below on the aryl moiety), (xvi) a saturated heterocyclic thio group (optionally having from 1 to 5

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substituents α_{1c} mentioned below), (xvii) a monocyclic heteroaromatic thio group (optionally having from 1 to 5 substituents α_{1c} mentioned below), (xviii) an amino group (optionally having one or two substituents α_{1c} mentioned below) or (xix) a hydroxyl group,

the substituent α_{1c} represents (i) a C_1 - C_6 alkyl group, (ii) a C_1 - C_6 halogenoalkyl group, (iii) a C_1 - C_6 alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a C_3 - C_{10} cycloalkyl group, (ix) a C_6 - C_{10} aryl group (optionally having from 1 to 5 substituents β_c mentioned below), (x) a C_7 - C_{16} aralkyl group (optionally having from 1 to 5 substituents β_c mentioned below on the aryl moiety), (xi) a C_1 - C_7 aliphatic acyl group, (xii) a C_4 - C_{11} cycloalkylcarbonyl group, (xiii) a C_7 - C_{11} arylcarbonyl group (optionally having from 1 to 5 substituents β_c mentioned below), (xiv) a C_8 - C_{17} aralkylcarbonyl group (optionally having from 1 to 5 substituents β_c mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β_c mentioned below), (xvi) a carbamoyl group, (xvii) a C_7 - C_{11}

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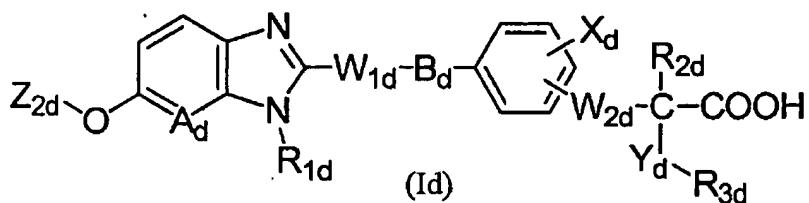
arylaminocarbonyl group (optionally having from 1 to 5 substituents β_c mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents β_c mentioned below) or (xix) a carboxyl group,

the substituent β_c represents (i) a C_1-C_{10} alkyl group, (ii) a halogen atom, (iii) a C_6-C_{10} aryl group (optionally having from 1 to 5 substituents γ_c mentioned below), (iv) a C_7-C_{16} aralkyl group (optionally having from 1 to 5 substituents γ_c mentioned below on the aryl moiety), (v) a C_1-C_7 aliphatic acyl group, (vi) a C_7-C_{11} arylcarbonyl group (optionally having from 1 to 5 substituents γ_c mentioned below), (vii) a C_8-C_{17} aralkylcarbonyl group (optionally having from 1 to 5 substituents γ_c mentioned below on the aryl moiety), (viii) a C_4-C_{11} cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents γ_c mentioned below), (x) a carbamoyl group or (xi) a C_7-C_{11} arylaminocarbonyl group (optionally having from 1 to 5 substituents γ_c mentioned below on the aryl moiety) and

the substituent γ_c represents a C_1-C_6 alkyl group, a C_1-C_6

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halogenoalkyl group, a halogen atom or a hydroxyl group],
 a α -substituted carboxylic acid derivative having the
 general formula (Id) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

R_{1d} , R_{2d} and R_{3d} are the same or different, and each represents (i) a hydrogen atom, (ii) a C_1-C_6 alkyl group, (iii) a C_6-C_{10} aryl group (optionally having from 1 to 5 substituents α_{1d} mentioned below), (iv) a C_7-C_{16} aralkyl group (optionally having from 1 to 5 substituents α_{1d} mentioned below on the aryl moiety), (v) a C_1-C_6 alkylsulfonyl group, (vi) a C_1-C_6 halogenoalkylsulfonyl group, (vii) a C_6-C_{10} arylsulfonyl group (optionally having from 1 to 5 substituents α_{1d} mentioned below)

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or (viii) a C₇-C₁₆ aralkylsulfonyl group (optionally having from 1 to 5 substituents α_{1d} mentioned below on the aryl moiety),

A_d represents a nitrogen atom or a =CH- group,

B_d represents an oxygen atom or a sulfur atom,

W_{1d} represents a C₁-C₈ alkylene group,

W_{2d} represents a single bond or a C₁-C₈ alkylene group,

X_d represents (i) a hydrogen atom, (ii) a C₁-C₆ alkyl group, (iii) a C₁-C₆ halogenoalkyl group, (iv) a C₁-C₆ alkoxy group, (v) a halogen atom, (vi) a hydroxyl group, (vii) a cyano group, (viii) a nitro group, (ix) a C₃-C₁₀ cycloalkyl group, (x) a C₆-C₁₀ aryl group (optionally having from 1 to 5 substituents β_d mentioned below), (xi) a C₇-C₁₆ aralkyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety),

(xii) a C₁-C₇ aliphatic acyl group, (xiii) a C₄-C₁₁ cycloalkylcarbonyl group, (xiv) a C₇-C₁₁ arylcarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below), (xv) a C₈-C₁₇ aralkylcarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety), (xvi) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β_d mentioned below), (xvii) a carbamoyl

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group, (xviii) a C₇-C₁₁ arylaminocarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety) or (xix) an amino group (optionally having one or two substituents β_d mentioned below),

Y_d represents an oxygen atom or a S(O)_p group (wherein p is an integer of from 0 to 2),

Z_{2d} represents a saturated heterocyclic group (optionally having from 1 to 5 substituents α_{1d} mentioned below) or a C₆-C₁₀ aryl group (optionally having from 1 to 5 substituents α_{2d} mentioned below),

the substituent α_{1d} represents (i) a C₁-C₆ alkyl group, (ii) a C₁-C₆ halogenoalkyl group, (iii) a C₁-C₆ alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a C₃-C₁₀ cycloalkyl group, (ix) a C₆-C₁₀ aryl group (optionally having from 1 to 5 substituents β_d mentioned below), (x) a C₇-C₁₆ aralkyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety), (xi) a C₁-C₇ aliphatic acyl group, (xii) a C₄-C₁₁ cycloalkylcarbonyl group, (xiii) a C₇-C₁₁ arylcarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below), (xiv) a C₈-C₁₇ aralkylcarbonyl

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group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β_d mentioned below), (xvi) a carbamoyl group, (xvii) a C₇-C₁₁ arylaminocarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents β_d mentioned below) or (xix) a carboxyl group,

the substituent α_{2d} represents (i) a C₃-C₁₀ cycloalkyl group, (ii) a C₆-C₁₀ aryl group (optionally having from 1 to 5 substituents β_d mentioned below), (iii) a C₇-C₁₆ aralkyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety), (iv) a C₁-C₇ aliphatic acyl group, (v) a C₄-C₁₁ cycloalkylcarbonyl group, (vi) a C₇-C₁₁ arylcarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below), (vii) a C₈-C₁₁ aralkylcarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety), (viii) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β_d mentioned below) or (ix) a C₇-C₁₁

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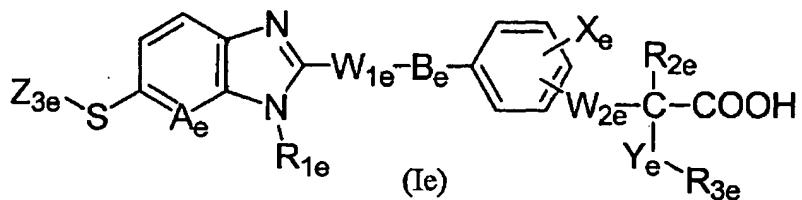
arylaminocarbonyl group (optionally having from 1 to 5 substituents β_d mentioned below on the aryl moiety),

the substituent β_d represents (i) a C_1-C_{10} alkyl group, (ii) a halogen atom, (iii) a C_6-C_{10} aryl group (optionally having from 1 to 5 substituents γ_d mentioned below), (iv) a C_7-C_{16} aralkyl group (optionally having from 1 to 5 substituents γ_d mentioned below on the aryl moiety), (v) a C_1-C_7 aliphatic acyl group, (vi) a C_7-C_{11} arylcarbonyl group (optionally having from 1 to 5 substituents γ_d mentioned below), (vii) a C_8-C_{17} aralkylcarbonyl group (optionally having from 1 to 5 substituents γ_d mentioned below on the aryl moiety), (viii) a C_4-C_{11} cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents γ_d mentioned below), (x) a carbamoyl group or (xi) a C_7-C_{11} arylaminocarbonyl group (optionally having from 1 to 5 substituents γ_d mentioned below on the aryl moiety) and

the substituent γ_d represents a C_1-C_6 alkyl group, a C_1-C_6 halogenoalkyl group, a halogen atom or a hydroxyl group} and a α -substituted carboxylic acid derivative having the

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general formula (Ie) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

R_{1e} , R_{2e} and R_{3e} are the same or different, and each represents (i) a hydrogen atom, (ii) a $\text{C}_1\text{-C}_6$ alkyl group, (iii) a $\text{C}_6\text{-C}_{10}$ aryl group (optionally having from 1 to 5 substituents α_{1e} mentioned below), (iv) a $\text{C}_7\text{-C}_{16}$ aralkyl group (optionally having from 1 to 5 substituents α_{1e} mentioned below on the aryl moiety), (v) a $\text{C}_1\text{-C}_6$ alkylsulfonyl group, (vi) a $\text{C}_1\text{-C}_6$ halogenoalkylsulfonyl group, (vii) a $\text{C}_6\text{-C}_{10}$ arylsulfonyl group (optionally having from 1 to 5 substituents α_{1e} mentioned below) or (viii) a $\text{C}_7\text{-C}_{16}$ aralkylsulfonyl group (optionally having from 1 to 5 substituents α_{1e} mentioned below on the aryl moiety),

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A_e represents a nitrogen atom or a =CH- group,
 B_e represents an oxygen atom or a sulfur atom,
 W_{1e} represents a C_1 - C_8 alkylene group,
 W_{2e} represents a single bond or a C_1 - C_8 alkylene group,
 X_e represents (i) a hydrogen atom, (ii) a C_1 - C_6 alkyl group,
(iii) a C_1 - C_6 halogenoalkyl group, (iv) a C_1 - C_6 alkoxy group, (v)
a halogen atom, (vi) a hydroxyl group, (vii) a cyano group,
(viii) a nitro group, (ix) a C_3 - C_{10} cycloalkyl group, (x) a C_6 - C_{10}
aryl group (optionally having from 1 to 5 substituents β_e
mentioned below), (xi) a C_7 - C_{16} aralkyl group (optionally having
from 1 to 5 substituents β_e mentioned below on the aryl moiety),
(xii) a C_1 - C_7 aliphatic acyl group, (xiii) a C_4 - C_{11}
cycloalkylcarbonyl group, (xiv) a C_7 - C_{11} arylcarbonyl group
(optionally having from 1 to 5 substituents β_e mentioned below),
(xv) a C_8 - C_{11} aralkylcarbonyl group (optionally having from 1 to 5
substituents β_e mentioned below on the aryl moiety), (xvi) a
monocyclic heteroaromatic carbonyl group (optionally having from
1 to 5 substituents β_e mentioned below), (xvii) a carbamoyl
group, (xviii) a C_7 - C_{11} arylaminocarbonyl group (optionally having
from 1 to 5 substituents β_e mentioned below on the aryl moiety)

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or (xix) an amino group (optionally having one or two substituents β_e mentioned below),

Y_e represents an oxygen atom or a $S(O)_p$ group (wherein p is an integer of from 0 to 2),

Z_{3e} represents (i) a C_1 - C_6 alkyl group, (ii) a C_6 - C_{10} aryl group (optionally having from 1 to 5 substituents α_{1e} mentioned below), (iii) a C_7 - C_{16} aralkyl group (optionally having from 1 to 5 substituents α_{1e} mentioned below on the aryl moiety), (iv) a C_3 - C_{10} cycloalkyl group or (v) a saturated heterocyclic group (optionally having from 1 to 5 substituents α_{1e} mentioned below),

the substituent α_{1e} represents (i) a C_1 - C_6 alkyl group, (ii) a C_1 - C_6 halogenoalkyl group, (iii) a C_1 - C_6 alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a C_3 - C_{10} cycloalkyl group, (ix) a C_6 - C_{10} aryl group (optionally having from 1 to 5 substituents β_e mentioned below), (x) a C_7 - C_{16} aralkyl group (optionally having from 1 to 5 substituents β_e mentioned below on the aryl moiety), (xi) a C_1 - C_7 aliphatic acyl group, (xii) a C_4 - C_{11} cycloalkylcarbonyl group, (xiii) a C_7 - C_{11} arylcarbonyl group (optionally having from 1 to 5 substituents β_e mentioned below), (xiv) a C_8 - C_{17} aralkylcarbonyl

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group (optionally having from 1 to 5 substituents β_e mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β_e mentioned below), (xvi) a carbamoyl group, (xvii) a C₇-C₁₁ arylaminocarbonyl group (optionally having from 1 to 5 substituents β_e mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents β_e mentioned below) or (xix) a carboxyl group,

the substituent β_e represents (i) a C₁-C₁₀ alkyl group, (ii) a halogen atom, (iii) a C₆-C₁₀ aryl group (optionally having from 1 to 5 substituents γ_e mentioned below), (iv) a C₇-C₁₆ aralkyl group (optionally having from 1 to 5 substituents γ_e mentioned below on the aryl moiety), (v) a C₁-C₇ aliphatic acyl group, (vi) a C₇-C₁₁ arylcarbonyl group (optionally having from 1 to 5 substituents γ_e mentioned below), (vii) a C₈-C₁₇ aralkylcarbonyl group (optionally having from 1 to 5 substituents γ_e mentioned below on the aryl moiety), (viii) a C₄-C₁₁ cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents γ_e mentioned below),

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(x) a carbamoyl group or (xi) a C₇-C₁₁ arylaminocarbonyl group
(optionally having from 1 to 5 substituents γ_e mentioned below on
the aryl moiety) and

the substituent γ_e represents a C₁-C₆ alkyl group, a C₁-C₆
halogenoalkyl group, a halogen atom or a hydroxyl group; and
wherein said diuretic is amiloride.

Claim 3 (Cancelled).

4. (Currently Amended). A pharmaceutical composition comprising
a diuretic and an insulin sensitizer in ratio of amount by weight
of 1:200 to 200:1, according to Claim 1 wherein said diuretic is
an ENaC inhibitor and said insulin sensitizer is 5-[4-(6-methoxy-
1-methyl-1H-benzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-
dione or a pharmacologically acceptable salt thereof.

Claim 5 (Cancelled).

6. (Original) A pharmaceutical composition according to Claim 4,
wherein said diuretic is amiloride.

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7. (Currently Amended) A pharmaceutical composition comprising a diuretic and an insulin sensitizer in a ratio of amounts by weight of 1:200 to 200:1 and according to claim 1, wherein said diuretic is amiloride.

8. (Withdrawn-Currently Amended) A method for the treatment or prophylaxis of diabetes mellitus, wherein said treatment or prophylaxis comprises administration in effective amounts, of the pharmaceutical composition of ~~claim 1~~ claim 3, 4, 6 or 7.

Claims 9-16 (Canceled).

17. (Withdrawn-Currently Amended) A method for the prophylaxis of edema, cardiac enlargement, body fluid retention, or hydrothorax caused by an insulin sensitizer comprising administering an effective amount of the pharmaceutical composition of ~~claim 1~~ claim 3, 4, 6 or 7.

Claims 18-21 (Canceled).